PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
PC-21013879		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/000879.	07.06.2004	03.07.2003
International Patent Classification (IPC) or national classification and IPC		
A61F2/04, A61L27/58		
Applicant		
Astra Tech AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.05.2005	14.10.2005
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Form PCT/IPEA/409 (cover sheet) (April 2005)

Absolute Translations

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/000879

Box No. I — Basis of the report

1. With regard to the **language**, this report is based on:

- [x] the international application in the language in which it was filed
- [ ] a translation of the international application into ____________________ , which is the language of a translation furnished for the purposes of:
  - [ ] international search (Rules 12.3(a) and 23.1(b))
  - [ ] publication of the international application (Rule 12.4(a))
  - [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

- [ ] the international application as originally filed/furnished
- [x] the description:
  - pages 1-27 as originally filed/furnished
  - pages* ________ received by this Authority on ________
  - pages* ________ received by this Authority on ________
- [x] the claims:
  - pages ________ as originally filed/furnished
  - pages* ________ as amended (together with any statement) under Article 19
  - pages* 28-36 received by this Authority on 02.05.2005
  - pages* ________ received by this Authority on ________
- [x] the drawings:
  - pages 1/1 as originally filed/furnished
  - pages* ________ received by this Authority on ________
  - pages* ________ received by this Authority on ________
- [ ] a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

- [ ] the description, pages ________
- [ ] the claims, Nos. ________
- [ ] the drawings, sheets/figs ________
- [ ] the sequence listing *(specify)*: ________
- [ ] any table(s) related to the sequence listing *(specify)*: ________

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages ________
- [ ] the claims, Nos. ________
- [ ] the drawings, sheets/figs ________
- [ ] the sequence listing *(specify)*: ________
- [ ] any table(s) related to the sequence listing *(specify)*: ________

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 48-56

because:

☒ the said international application, or the said claims Nos. 48-56 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/00879

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-47	YES
	Claims		NO
Inventive step (IS)	Claims	1-47	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-47	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Amended claims 1-56 were filed on 02.05.2005.

Documents cited in the International Search Report:

D1: EP 0945145 A1
D2: US 6548569 B1
D3: US 5358475 A1
D4: US 5735863 A1

The cited documents represent the general state of the art. The invention defined in claims 1-47 is not disclosed by any of the documents D1-D4.
The cited prior art does not give any indication that would lead a person skilled in the art to the claimed device, where the guiding means presents an in vivo degradation time being less than the time required for establishing contact between the ends of a nerve. Therefore, the claimed invention is not obvious to a person skilled in the art.
Accordingly, the device, the kit and the sheet defined in claims 1-47 are novel and are considered to involve an inventive step. The invention is industrially applicable.

CLAIMS

1. A device for promoting regeneration of an injured nerve comprising a nerve encasement structure and a plurality of biodegradable guiding means c h a r a c t e r i z e d in that at least a majority of the guiding means presents an in vivo degradation time t_1 being less than a time t_c required for establishing regenerated contact between the ends of an injured nerve using the device for said regeneration.

2. A device according to claim 1, wherein at least a major part of the nerve encasement structure presents an in vivo degradation time t_2 being longer than t_1 ($t_2 > t_1$).

3. A device according to claim 2, wherein t_2 is longer than a time t_r required for the entire nerve regeneration process to be completed ($t_2 > t_r$).

4. A device for promoting regeneration of an injured nerve comprising a biodegradable nerve encasement structure, and a plurality of biodegradable guiding means, c h a r a c t e r i z e d in that at least a majority of the guiding means presents an in vivo degradation time t_1, at least a major part of the nerve encasement structure presents an in vivo degradation time t_2, t_2 being longer than t_1 ($t_2 > t_1$) and longer than a time t_r required for the entire nerve regeneration process to be completed ($t_2 > t_r$), and t_1 being less than t_r ($t_1 < t_r$).

5. A device according to claim 4, wherein t_1 is less than a time t_c required for establishing regenerated contact between the ends of an injured nerve using the device for said regeneration.

6. A device according to any one of the preceding claims, wherein the plurality of biodegradable guiding means are a plurality of biodegradable guiding fibres.

7. A device according to any one of the preceding claims, wherein the material of the nerve encasement structure and the material of the guiding means each comprises one or more biodegradable polymers.

8. A device according to claim 7, wherein said one or more biodegradable polymers comprise(s) one or more biodegradable polyesters.

9. A device according to claim 8, wherein said one or more biodegradable polyesters comprise(s) PHB.

10. A device according to claim 8, wherein the material of the nerve encasement structure comprises PHB and the material of the guiding means comprises PHB.

11. A device according to claim 8, wherein the material of the nerve encasement structure comprises PHB and the material of the guiding means comprises PLGA.

12. A device according to any one of claims 7-11, wherein said one or more polymers comprised in the material of the guiding means present an average molecular weight which is lower than an average molecular weight of said one or more polymers comprised in the material of the nerve encasement structure.

13. A nerve regeneration device according to claim 12, wherein the material of the nerve encasement structure and the material of the guiding means each comprises PHB having an average molecular weight within the range of from 50 000 to 500 000.

14. A device according to claim 13, wherein the PHB average molecular weight of the nerve encasement structure is within the range of from 100 000 to 250 000 and the PHB average molecular weight of the guiding means is within the range of from 50 000 to < 250 000.

15. A device according to any one of the preceding claims, wherein the nerve encasement structure comprises a compressed non-woven sheet of biodegradable fibres having an essentially unidirectional fibre orientation.

16. A device according to any one of the preceding claims, wherein the plurality of guiding means are biodegradable fibres in the form of a non-bonded fibre web having an essentially unidirectional fibre orientation.

17. A device according to any one of the preceding claims, further comprising a hydrogel matrix.

18. A device according to any one of the preceding claims, further comprising one or more biologically active substances or cells.

19. A device according to claim 18, wherein said one or more biologically active substances comprises a nerve growth promoting substance selected from the group consisting nerve growth factor (NGF); brain-derived neurotrophic factor (BDNF); neurotrophin-3 (NT-3); neurotrophin-4 (NT-4); glial growth factor (GGF); insulin-like growth factor (IGF); platelet-derived growth factor (PDGF); fibroblast growth factor (FGF); transforming growth factor (TGF); and epidermal growth factor (EGF).

20. A device according to claim 18, wherein said one or more biologically active cells is selected from the group consisting of endothelial cells; fibroblasts;

Schwann cells; olfactory ensheathing cells; stem cells or precursor cells thereof.

21. A device according to any one of the preceding claims, wherein the guiding means occupies ≤ 2.0% by volume of the lumen formed by the nerve encasement structure.

22. A device according to any one of the preceding claims, wherein each guiding means of a majority of the guiding means has a cross-sectional dimension ≤ 50 μm.

23. A device according to claim 22, wherein each guiding means of a majority of the guiding means has a cross-sectional dimension ≤ 20 μm.

24. A device according to claim 23, wherein each guiding means of a majority of the guiding means has a cross-sectional dimension within the range of from 5 to 15 μm.

25. A kit for preparing a device for promoting regeneration of an injured nerve, said kit comprising a sheet and a plurality of biodegradable guiding means, c h a r a c t e r i z e d in that at least a majority of the guiding means presents an in vivo degradation time t_1 being less than a time t_c required for establishing regenerated contact between the ends of an injured nerve using the device for said regeneration.

26. A kit according to claim 25, wherein the sheet presents an in vivo degradation time t_2 being longer than t_1 ($t_2 > t_1$).

27. A kit for preparing a device for promoting regeneration of an injured nerve, said kit comprising a biodegradable sheet and a plurality of biodegradable

guiding means, c h a r a c t e r i z e d in that at least a majority of the guiding means presents an in vivo degradation times t_1, at least a major part of the sheet presents an in vivo degradation time t_2, t_2 being longer than t_1 ($t_2 > t_1$) and longer than a time t_r required for the entire nerve regeneration process to be completed ($t_2 > t_r$), and t_1 being less than t_r ($t_1 < t_r$).

28. A kit according to any one of claims 25-27, wherein the plurality of biodegradable guiding means are a plurality of biodegradable guiding fibres.

29. A kit according to any one of claims 25-28, wherein the material of the sheet and the material of the guiding means each comprises one or more biodegradable polymers.

30. A kit according to claim 29, wherein said one or more biodegradable polymer comprises one or more biodegradable polyester.

31. A kit according to claim 30, wherein said one or more biodegradable polyester comprises PHB.

32. A kit according to claim 30, wherein the material of the sheet comprises PHB and the material of the guiding means comprises PHB.

33. A kit according to claim 30, wherein the material of the sheet comprises PHB and the material of the guiding means comprises PLGA.

34. A kit according to any one of claims 29-33, wherein said one or more polymers comprised in the material of the guiding means present an average molecular weight which is lower than an average molecular weight of

said one or more polymers comprised in the material of the sheet.

35. A kit according to claim 34, wherein the material of the and the material of the guiding means each comprises PHB having an average molecular weight within the range of from 50 000 to 500 000.

36. A kit according to claim 35, wherein the PHB molecular weight of the sheet is within the range of from 100 000 to 250 000 and the PHB molecular weight of the guiding means is within the range of from 50 000 to < 250 000.

37. A kit according to any one of claims 25-36, wherein the sheet comprises a compressed non-woven sheet of biodegradable fibres having an essentially unidirectional fibre orientation.

38. A kit according to any one of claims 25-37, wherein the plurality of guiding means are biodegradable fibres in the form of a non-bonded fibre web having an essentially unidirectional fibre orientation.

39. A kit according to any one of claims 25-38, further comprising a hydrogel material.

40. A kit according to claim 39, wherein the hydrogel is in a dehydrated state.

41. A kit according to any one of claims 25-40, further comprising one or more biologically active substances or cells.

42. A kit according to claim 41, wherein said one or more biologically active substance comprises a nerve growth promoting substance selected from the group con-

sisting of nerve growth factor (NGF); brain-derived neurotrophic factor (BDNF); neurotrophin-3 (NT-3); neurotrophin-4 (NT-4); glial growth factor (GGF); insulin-like growth factor (IGF); platelet-derived growth factor (PDGF); fibroblast growth factor (FGF); transforming growth factor (TGF); and epidermal growth factor (EGF).

43. A kit according to claim 41, wherein said one or more biologically active cells is selected from the group consisting of endothelial cells; fibroblasts; Schwann cells; olfactory ensheathing cells; stem cells or precursor cells thereof.

44. A biodegradable sheet for preparing a device for promoting regeneration of an injured nerve, c h a r a c t e r i z e d in having at least one surface at least partly coated with a dehydrated hydrogel material and a plurality of biodegradable guiding means, wherein at least a majority of the guiding means presents an in vivo degradation time t_1 being less than a time t_c required for establishing regenerated contact between the ends of an injured nerve using device.

45. A biodegradable sheet for preparing a device for promoting regeneration of an injured nerve, c h a r a c t e r i z e d in having at least one surface at least partly coated with a dehydrated hydrogel material and a plurality of biodegradable guiding means, wherein at least a majority of the guiding means presents an in vivo degradation time t_1, at least a major part of the sheet presents an in vivo degradation time t_2, t_2 being longer than t_1 ($t_2 > t_1$) and longer than a time t_r required for the entire nerve regeneration process to be completed ($t_2 > t_r$), and t_1 being less than t_r ($t_1 < t_r$).

46. A biodegradable sheet according to claim 44 or claim 45, wherein the plurality of biodegradable guiding means are a plurality of biodegradable guiding fibres.

47. A biodegradable sheet according to any one of claims 44-46, said dehydrated hydrogel material further comprising one or more biologically active substances or cells.

48. Use of a plurality of biodegradable guiding means for promoting regeneration of an injured nerve, c h a r a c t e r i z e d in that at least a majority of the guiding means presents an in vivo degradation time t_1 being less than a time t_c required for establishing regenerated contact between the ends of an injured nerve using the guiding means for said regeneration.

49. Use according to claim 48, wherein the plurality of biodegradable guiding means are a plurality of biodegradable guiding fibres.

50. Use according to claim 48 or claim 49, wherein the material of the guiding means comprises one or more biodegradable polymers.

51. Use according to claim 50, wherein said one or more biodegradable polymer comprises one or more biodegradable polyesters.

52. Use according to claim 51, wherein said one or more biodegradable polyesters comprises PHB.

53. Use according to claim 51, wherein said one or more biodegradable polyesters comprises PLGA.

54. Use according to claim 52, wherein PHB has an average molecular weight within the range of from 50 000 to 250 000.

55. Use according to any one of claims 48-54, wherein the guiding means are fibres in the form of a non-bonded fibre web having an essentially unidirectional fibre orientation.

56. A method for promoting regeneration of an injured nerve c h a r a c t e r i z e d in comprising the step of applying at said injured nerve a device according to any one of claims 1-24.